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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,265	ALTHOFER ET AL.	
	Examiner	Art Unit	
	Christian L Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,19 and 20* is/are pending in the application.

4a) Of the above claim(s) *1, 6-10, 19, 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/11/02, 5/23/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. Applicants' election with traverse of Group III, claim 14, and amendments to claims 2-5 and 11-15 in the reply filed on 7/19/2004, is acknowledged.

Applicants have not presented arguments to traverse the lack of unity of invention stated in the previous Office Action dated 6/15/2004, and have instead requested that claims which are amended to depend from claim 14 be examined with elected claim 14. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

In view of applicants' amendments to the claims, the instant application now contains four inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I	Claim 1, drawn to a monocellular or multicellular organism.
Group II	Claims 6-10, drawn to an isocitrate dehydrogenase gene, vector, and transformed organism containing said isocitrate dehydrogenase gene.
Group III	Claims 2-5 and 11-17, drawn to a process for the production of riboflavin.
Group IV	Claims 19 and 20, drawn to a use of an isocitrate dehydrogenase gene or vector for preparing an organism.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

A same or corresponding technical feature shared among Groups I-IV is a gene encoding an isocitrate dehydrogenase and its allelic variations. However, this technical feature has already been taught in the prior art by Henke et al. (reference of record cited in the IDS filed 2/11/2002).

Henke et al. teach the IDP3 gene which encodes a NADP-dependent isocitrate dehydrogenase (see entire publication, especially Fig. 3 on p. 3705). Since the specification (see p.6, line 37 to p. 7, line 5) states that allelic variations include deletions, insertions, and substitutions of nucleotides in the nucleotide sequence of the isocitrate dehydrogenase gene of SEQ ID NO: 1, then the IDP3 gene taught by Henke et al., which has deletions, insertions, and substitutions of nucleotides of SEQ ID NO: 1, is deemed to be an allelic variation of the

isocitrate dehydrogenase gene shared among Groups I-IV

Thus, the technical feature is not special since it was known in the prior art and therefore cannot form the contribution that the group of inventions as a whole makes over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 2-5 and 11-17 are under consideration in this Office Action in view of applicants' amendment to the claims and election of claim 14.

3. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

4. The paper copy and computer readable form (CRF) of the Sequence Listing filed 2/11/2002 have been received and have been processed by the Scientific and Technical Information Center (STIC).

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: A process for the biotechnological production of riboflavin.

6. The disclosure is objected to because of the following informality: in the specification there is no statement that indicates that the instant application is the US National Stage filing of PCT Application No. PCT/EP00/07370, filed July 31, 2000, which claims foreign priority under 35 U.S.C. 119(a)-(d) to foreign patent application 199 37 548.8 filed in Germany on August 9, 1999. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. Appropriate correction is required.

7. Foreign patent EP 0927761 A2 cited in the IDS filed 2/11/2002 and foreign patents DE 19840709 A1 and DE 19545468 A1 cited in the IDS filed 5/23/2002 have not been considered because a concise explanation of its relevance has not been provided and an English-language translation of these non-English-language patents have not been provided.

8. The references of Windholz et al. and Bacher et al. cited in the IDS filed 5/23/2002 have not been considered because copies of these references have not been provided by applicants.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 2-5 and 11-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "exhibits" in claim 2, line, 3, is vague and indefinite since it is not clear as to whether the recited microorganism is claimed to have or possess an "elevated isocitrate dehydrogenase activity". The term "elevated " in claim 2, line 3, is a relative term which renders the claim indefinite. The term "elevated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. The metes and bounds of the term "elevated" cannot be determined since there is no recitation of a companion of the "elevated isocitrate dehydrogenase activity" to the activity of a wild-type isocitrate dehydrogenase. See MPEP § 2173.05(b).

In claim 11, line 7, the phrase "whose copy number is increased" renders the claim vague and indefinite because it is not clear if applicants intended that the microorganism harboring the claimed gene encoding isocitrate dehydrogenase is to be compared to a microorganism having a gene encoding isocitrate dehydrogenase whose copy number is not increased.

Regarding claim 12, the phrase "vector which contains such" in line 5 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

In claim 13, line 3, the phrase "isocitrate dehydrogenase gene which exhibits a catalytic activity which is increased, and/or an ability to be inhibited by inhibitors which is decreased" renders the claim vague and indefinite since it is not clear as to whether the recited microorganism is claimed to have or possess an increased catalytic activity or decreased ability to be inhibited by inhibitors; and it is not clear how a gene, rather than the enzyme encoded by the gene, can in fact have the recited increased catalytic activity or decreased ability to be inhibited.

In claim 14, line 2, the term "exhibits" renders the claim vague and indefinite since it is not clear as to whether the recited microorganism is claimed to have or possess an increased

activity of a NAD(P)H-forming enzyme . In claim 14, line 5, the phrase "wild type of the species Ashbya gossypii ATCC 10895" renders the claim vague and indefinite because Ashbya gossypii ATCC 10895 is a strain and not a species, and it is uncertain what a "wild type" of a strain is intended to denote. Claims 2-5 and 11-13 which depends from claim 14 are also rejected because they do not correct the defect of claim 14.

In claim 15, line 5, the phrase "wild type of the species Ashbya gossypii ATCC 10895" renders the claim vague and indefinite because Ashbya gossypii ATCC 10895 is a strain and not a species, and it is uncertain what a "wild type" of a strain is intended to denote. Claims 16 and 17 which depends from claim 15 are also rejected because they do not correct the defect of claim 15.

Claim 17 recites the limitation "isocitrate dehydrogenase" in lines 2-4. There is insufficient antecedent basis for this limitation in the claim.

11. Claims 2-5 and 11-17 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are culturing or fermenting the microorganism in a suitable medium containing the appropriate substrates to produce riboflavin and recovering or isolating the produced riboflavin from the medium.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 2-5 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 14 and 15 encompass methods for making riboflavin using any microorganism which exhibits an activity of any NAD(P)H-forming enzyme that is higher than a wild-type Ashbya gossypii species. For examination purposes, the recited microorganism is claimed to have or possess an increased activity of a NAD(P)H-forming enzyme that is higher than a wild-type Ashbya gossypii species. The scope of the claim includes many enzymes with widely differing biological functions and widely differing structural, chemical, and physical characteristics. Furthermore, the genus is highly variable because a significant number of structural differences between genus members is permitted.

The specification discloses an Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2. However, the specification fails to provide a written description of additional NAD(P)H -forming enzymes as encompassed by the claimed genus. Neither the specification nor the general knowledge of those skilled in the art provide evidence of any structure which would be expected to be common to the members of the genus. Thus, the disclosed isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 is not representative of the claimed genus since other members of the genus have biological functions, amino acid sequences, and structures that are different from the said Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of the necessary common features or attributes possessed by members of the genus, and thus has failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention of claims 14 and 15. Claims 3-5 which depend from claim 14 and claim 16 which depends from claim 15 are also rejected because they do not correct the defect of claim 14 and claim 15, respectively.

Claim 2 encompasses methods for making riboflavin using any microorganism which exhibits any elevated isocitrate dehydrogenase activity. For examination purposes, the recited microorganism is assumed to have and possess any elevated activity of any isocitrate dehydrogenase. Claim 2 is a genus claims that are directed toward all isocitrate dehydrogenase from any biological source having any amino acid sequence and structure, where its enzymatic activity is elevated by any genetic modification or manipulation. The scope of the claim includes many isocitrate dehydrogenase enzymes with widely differing structural, chemical, and physical characteristics, where the genus is highly variable because a significant number of structural differences between genus members is permitted. Furthermore, the scope of the claim includes many genetic modification which result in an elevated enzymatic activity.

The specification discloses an Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2. However, the specification fails to provide a written description of additional isocitrate dehydrogenase enzymes as encompassed by the claimed

genus. Neither the specification nor the general knowledge of those skilled in the art provide evidence of any structure which would be expected to be common to the members of the genus. Thus, the disclosed isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 is not representative of the claimed genus since other members of the genus have amino acid sequences and structures that are different from the said Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2. Furthermore, the specification only discloses transforming a host cell with a polynucleotide encoding SEQ ID NO: 2, where the said polynucleotide is over expressed under the control of a strong TEF promoter (see p. 8-9 of specification).

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of the necessary common features or attributes possessed by members of the genus, and thus has failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention of claim 2.

Claims 11 and 12 encompass methods for making riboflavin using any microorganism having any allelic variant of any gene encoding an isocitrate dehydrogenase having the amino acid sequence of SEQ ID NO: 2 . Claims 11 and 12 are genus claims that are directed toward all allelic variants of any gene encoding any isocitrate dehydrogenase having the amino acid sequence of SEQ ID NO: 2.

The ordinary meaning of the term allele is one of two or more alternate forms of a gene occupying the same locus in a particular chromosome or linkage structure and differing from other alleles of the locus at one or more mutational sites (see Rieger *et al.*, ***Glossary of genetics : classical and molecular*** 5th ed., New York: Springer-Verlag, 1991, pages 16-17). The claimed alleles in claims 11 and 12 are "strictly neutral" because they encode identical proteins, and make no difference to phenotype (see Rieger et al., p. 17). Hence, claims 11 and 12 include genes having naturally occurring mutational site(s). Furthermore, the specification on p. 6, line 38 to p. 7, line 5, states that allelic variations include derivatives that are obtainable by deletion, insertion, and substitution of nucleotides in polynucleotides that encode polypeptides with the "isocitrate dehydrogenase activity being preserved".

The specification, however, discloses only one allele within the scope of the genus: SEQ ID NO: 1. There is no description of the mutational sites that exist in nature, and there is no description of how the structure of SEQ ID NO: 1 relates to the structure of any "strictly neutral" alleles. The general knowledge in the art concerning alleles does not provide any indication of how the structure of one allele is representative of unknown alleles. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others. The common attributes of the claimed genus are not described. One of skill in the art would conclude that applicant was not in possession of the

claimed genus of claims 11 and 12 because a description of only one member of a genus is not representative of the variants of the genus and is insufficient to support the claim.

Furthermore, the scope of claims 11 and 12 includes many isocitrate dehydrogenase genes with widely differing structural, chemical, and physical characteristics from many biological sources. The genus is highly variable because a significant number of structural differences between genus members is permitted.

Elements which are not particularly described, including regulatory elements and untranslated regions, are essential to the function of the recited isocitrate dehydrogenase gene because the definition of "gene" requires them. Furthermore, an isolated polynucleotide encoding a isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 or an isolated polynucleotide consisting of the nucleotide sequence SEQ ID NO: 1 is disclosed as being essential to the function of the claimed invention.

The art indicates that the structure of genes with regulatory elements and untranslated regions is empirically determined. For example, the structural elements of "gene" mediating the expression of a particular protein in the liver may be different than the structural elements of the "gene" mediating the expression of the same protein in the brain. Therefore, the structure of these elements which applicants considers as being essential to the function of the claim are not conventional in the art.

There is no known or disclosed correlation between an isolated polynucleotide encoding a isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 or an isolated polynucleotide consisting of the nucleotide sequence SEQ ID NO: 1 and the structure of the non-described regulatory elements and untranslated regions of the gene. Furthermore, there is no additional disclosure of physical and/or chemical properties. In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of the genus of isocitrate dehydrogenase genes.

Claims 13 and 17 encompass methods for making riboflavin using any microorganism having any gene encoding any isocitrate dehydrogenase which exhibits a catalytic activity which is increased and/or decreased ability to be inhibited by inhibitors when compared to a microorganism that is not genetically altered. For examination purposes, the recited microorganism is assumed to have and possess any gene encoding any isocitrate dehydrogenase having an increased catalytic activity and/or decreased ability to be inhibited by inhibitors when compared to a microorganism that is not genetically altered.

Claims 13 and 17 are genus claims that are directed toward all isocitrate dehydrogenase from any biological source having any amino acid sequence and structure, where its catalytic activity is increased and/or its ability to be inhibited by inhibitors is decreased when compared to a microorganism that is not genetically altered. The scope of the claim includes many isocitrate dehydrogenase enzymes with widely differing structural, chemical, and physical characteristics.

Furthermore, the genus is highly variable because a significant number of structural differences between genus members is permitted.

The specification discloses an Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2. However, the specification fails to provide a written description of additional isocitrate dehydrogenase enzymes as encompassed by the claimed genus. Neither the specification nor the general knowledge of those skilled in the art provide evidence of any structure which would be expected to be common to the members of the genus. Thus, the disclosed isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 is not representative of the claimed genus since other members of the genus have amino acid sequences and structures that are different from the said Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2.

In view of the above considerations, one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by members of the genus since the disclosed Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 is not representative of the claimed genus. Accordingly, Applicant has failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicant was in possession of the claimed invention of claims 13 and 17.

14. Claims 2-5 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing riboflavin using a microorganism that is transformed with an isolated polynucleotide encoding an isocitrate dehydrogenase comprising the amino acid sequence of SEQ ID NO: 2 or an isolated polynucleotide of SEQ ID NO: 1 encoding an isocitrate dehydrogenase, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of claim 14 encompass methods for making riboflavin using any microorganism which has or possess any increased activity of any NAD(P)H-forming enzyme that is higher than a wild-type Ashbya gossypii species, where the any NAD(P)H-forming

enzyme is from any biological source, is of any structure and any amino acid sequence, and its increased activity is due to any genetic modification.

In order to meet the enablement requirement, one skilled in the art must be able to make the recited microorganism which has or possess any increased activity of any NAD(P)H-forming enzyme that is higher than a wild-type Ashbya gossypii species without undue experimentation using the specification coupled with information known in the art. However, neither the specification nor the general knowledge of those skilled in the art provide guidance or prediction on making any microorganism having or possessing any increased activity of any NAD(P)H-forming enzyme that is higher than a wild-type Ashbya gossypii species without undue experimentation.

The specification discloses an Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 which is encode by a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1. The specification discloses transformation of wild-type Ashbya gossypii host cells with the said polynucleotide of SEQ ID NO: 1 under control of a strong promoter, and the greater production of riboflavin as compared to untransformed wild-type Ashbya gossypii host cells. The specification does not provide guidance or prediction regarding how to make any microorganism having or possessing any increased activity of any other NAD(P)H-forming enzyme, where the any NAD(P)H-forming enzyme is from any biological source and is of any structure and any amino acid sequence.

Hence, one must perform an enormous amount of trial and error experimentation to determine the specific NAD(P)H-forming enzyme which can transformed into any microorganism for use in the production of riboflavin. Such trial and error experimentation is well outside the realm of routine experimentation and entails searching and screening a vast number of biological sources for any biological source containing any NAD(P)H-forming enzyme, isolating the polynucleotide encoding the NAD(P)H-forming enzyme of any amino acid sequence and structure, altering the polynucleotide using any genetic modification, transforming any microorganism with the genetically altered polynucleotide, and determining whether the transformed microorganism has an increased activity of the NAD(P)H-forming enzyme and can produce riboflavin. Teaching from the specification regarding screening and searching for the claimed invention is not guidance for making the claimed invention.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific identity of the NAD(P)H-forming enzyme and its amino acid sequence and structure. Without such a guidance, the amount of experimentation left to those skilled in the art to make the invention of claim14 is undue and well outside of routine experimentation. Claims 3-5, 15, and 16 which depend from claim 14 are also rejected because they do not correct the defect of claim 14.

The nature and breadth of claim 2 encompass methods for making riboflavin using any microorganism which has or possess any elevated activity of any isocitrate dehydrogenase of any amino acid sequence and structure from any biological source, where the elevated activity is due to any genetic modification.

In order to meet the enablement requirement, one skilled in the art, using the specification coupled with information known in the art, must be able to make the recited microorganism which has or possess any elevated activity of any isocitrate dehydrogenase of any amino acid sequence and structure from any biological source, where the elevated activity is due to any genetic modification. However, neither the specification nor the general knowledge of those skilled in the art provide guidance or prediction on making any microorganism having or possessing any elevated activity of any isocitrate dehydrogenase of any amino acid sequence and structure from any biological source, where the elevated activity is due to any genetic modification.

The specification discloses an Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 which is encode by a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1. The specification discloses transformation of wild-type Ashbya gossypii host cells with the said polynucleotide of SEQ ID NO: 1 under control of a strong promoter, and the greater production of riboflavin as compared to untransformed wild-type Ashbya gossypii host cells. The specification does not provide guidance or prediction regarding how to make any microorganism having or possessing any elevated activity of any isocitrate dehydrogenase of any amino acid sequence and structure from any biological source, where the elevated activity is due to any genetic modification.

Such trial and error experimentation is well outside the realm of routine experimentation and entails searching and screening a vast number of biological sources for any biological source containing any isocitrate dehydrogenase, isolating the polynucleotide encoding the isocitrate dehydrogenase of any amino acid sequence and structure, altering the polynucleotide using any genetic modification, transforming any microorganism with the genetically altered polynucleotide, and determining whether the transformed microorganism has an elevated isocitrate dehydrogenase activity and can produce riboflavin. Teaching from the specification regarding screening and searching for the claimed invention is not guidance for making the claimed invention.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific amino acid sequence and structure of the isocitrate dehydrogenase which has an elevated activity. Without such a guidance, the amount of experimentation left to those skilled in the art to make the invention of claim 2 is undue and well outside of routine experimentation.

The nature and breadth of claims 11 and 12 encompass methods for making riboflavin

using any microorganism which harbors any allelic variation of a polynucleotide which encodes an isocitrate dehydrogenase having the amino acid sequence of SEQ ID NO: 2, where the recited allelic variation encompasses derivatives obtainable by deletion, insertion, and substitution of any nucleotides in said polynucleotides that encode an isocitrate dehydrogenase having the amino acid sequence of SEQ ID NO: 2 (see specification on p. 6, line 38 to p. 7, line 5).

In order to meet the enablement requirement, one skilled in the art must be able to make the recited allelic variations encompassing derivatives obtainable by deletion, insertion, and substitution of any nucleotides in said polynucleotides that encode an isocitrate dehydrogenase having the amino acid sequence of SEQ ID NO: 2 without undue experimentation using the specification coupled with information known in the art. However, neither the specification nor the general knowledge of those skilled in the art provide guidance or prediction on making these allelic variations without undue experimentation.

The specification discloses an Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 which is encode by a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1. However, the specification does not provide guidance or prediction regarding the specific nucleotides that can be changed (deletion, insertion, substitution, additions or combinations thereof) which will result in an allelic variation that still encodes a functional isocitrate dehydrogenase.

The general knowledge of those skilled in the art does not provide any guidance or prediction regarding the specific nucleotides that can be changed (deletion, insertion, substitution, additions or combinations thereof) which will result in an allelic variation that still encodes a functional isocitrate dehydrogenase. The nature of alleles is that they are variant structures, and in the present state of the art the structure of one does not provide guidance to the structure of others.

Hence, one must perform an enormous amount of trial and error experimentation to determine the specific nucleotides that can be changed (deletion, insertion, substitution, additions or combinations thereof) which will result in an allelic variation that still encodes a functional isocitrate dehydrogenase. Such trial and error experimentation is well outside the realm of routine experimentation and entails selecting any one or more of the nucleotides in any polynucleotide encoding SEQ ID NO: 2 and searching and screening for the type of modification to perform on the selected nucleotide(s) (deletion, insertion, substitution, additions or combinations thereof) which will not result in a loss of enzyme activity, but instead result in an enzymatically active isocitrate dehydrogenase. Teaching regarding screening and searching for the claimed invention using enzyme assays stated in the specification is not guidance for making the claimed invention.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid residues which can be changed without inactivating enzyme activity. Without such a guidance, the amount of experimentation left to those skilled in

the art to make the invention of claims 11 and 12 is undue and well outside of routine experimentation.

The nature and breadth of claims 13 and 17 encompass methods for making riboflavin using any microorganism having any gene encoding any isocitrate dehydrogenase which has a catalytic activity that is increased and/or decreased ability to be inhibited by inhibitors when compared to a microorganism that is not genetically altered.

In order to meet the enablement requirement, one skilled in the art must be able to make the recited gene encoding any isocitrate dehydrogenase having an increased catalytic activity and/or decreased ability to be inhibited by inhibitors without undue experimentation using the specification coupled with information known in the art. However, neither the specification nor the general knowledge of those skilled in the art provide guidance or prediction on making the gene encoding any isocitrate dehydrogenase having an increased catalytic activity and/or decreased ability to be inhibited by inhibitors without undue experimentation.

The specification discloses an Ashbya gossypii isocitrate dehydrogenase consisting of the amino acid sequence of SEQ ID NO: 2 which is encode by a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 1.

However, the specification does not provide guidance or prediction regarding the specific amino acids residues in SEQ ID NO: 2 that are essential for enzyme activity which cannot be altered. Nor does the specification provide guidance or prediction regarding the specific amino acid residues in SEQ ID NO: 2 that can be changed that will result in an isocitrate dehydrogenase having an increased catalytic activity and/or decreased ability to be inhibited by inhibitors.

The general knowledge of those skilled in the art does not provide any guidance or prediction regarding amino acids residues in SEQ ID NO: 2 which cannot be altered, and specific amino acid residues in SEQ ID NO: 2 that can be changed that will result in an isocitrate dehydrogenase having an increased catalytic activity and/or decreased ability to be inhibited by inhibitors. The prior art as exemplified by Broun et al. (Science. 1998 Nov 13;282(5392):1315-7) teach that minor modifications to a protein sequence can completely alter the function of a protein. Broun et al. show that as few as four amino acid substitutions in a polypeptide consisting of 380 amino acid residues changes the enzymatic activity of the polypeptide from a desaturase to a hydroxylase (seen entire publication, especially the abstract and pp. 1316-1317).

Since neither the specification nor information known in the art provide guidance or prediction for the specific amino acid residues in SEQ ID NO: 2 which cannot be altered and specific amino acid residues in SEQ ID NO: 2 that can be changed that will result in an isocitrate dehydrogenase having an increased catalytic activity and/or decreased ability to be inhibited by inhibitors, one must perform an enormous amount of trial and error experimentation to determine the specific amino acid residues in SEQ ID NO: 2 that can be changed that will result in an

isocitrate dehydrogenase having an increased catalytic activity and/or decreased ability to be inhibited by inhibitors.

Such trial and error experimentation is well outside the realm of routine experimentation and entails selecting any one or more of the 183 amino acid residues in SEQ ID NO:2 to modify, searching and screening for the type of modification to perform on the selected amino acid residue(s) (deletion, insertion, substitution, additions or combinations thereof) which will not result in a loss of enzyme activity, but instead result in an isocitrate dehydrogenase having an increased catalytic activity and/or decreased ability to be inhibited by inhibitors, and then synthesizing the corresponding polynucleotide encoding the polypeptide. Teaching regarding screening and searching for the claimed invention using enzyme assays stated in the specification is not guidance for making the claimed invention.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid residues which can be changed without inactivating enzyme activity. Without such a guidance, the amount of experimentation left to those skilled in the art to make the invention of claims 13 and 17 is undue and well outside of routine experimentation.

Claim Rejections - 35 U.S.C. § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 3-5 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Revuelta Doval et al (US Patent 5,821,090; PTO 892).

Revuelta Doval et al. teach a recombinant process for making riboflavin which comprises using a Ashbya gossypii host organism transformed with an expression vector containing a polynucleotide consisting of the nucleotide sequence of SEQ ID NO: 11 (rib 7 gene) encoding the Ashbya gossypii HTP reductase (rib 7 gene product) consisting of the amino acid sequence of SEQ ID NO: 12 (see entire patent especially column 2, line 1 to column 7, line 26; column 3, lines 54-67; TABLE 6; and claim 9).

HTP reductase is known in the prior art as an enzyme that catalyzes the reversible conversion of 5-amino-6-(5-phosphoribitylamino) uracil and NADP+ to 5-amino-6-(5-phosphoribosylamino) uracil and NADPH (see attached NiceProt View of Swiss-

Prot: P33312).

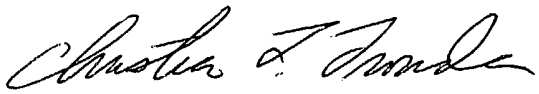
Hence, the HTP reductase taught by Revuelta Doval is deemed to fall within the scope and limitation of an "NADPH-forming enzyme" since the HTP reductase catalyzes the formation of NADPH; and the transformed Ashbya gossypii host organism taught by Revuelta Doval is deemed to fall within the scope and limitation of a microorganism which exhibits a higher NADPH-forming enzyme activity compared to a wild type Ashbya gossypii since the said transformed Ashbya gossypii host organism has an increased gene copy number of the rib 7 gene due to the expression vector containing the rib 7 gene of nucleotide sequence SEQ ID NO: 11, which is inserted into the said transformed Ashbya gossypii host organism. Thus, the reference teachings of Revuelta Doval et al. anticipate claims 3-5 and 14-16.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Christian L. Fronda
Art Unit 1652

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